REMARKS

I. Status of the Claims.

Claims 1-14, 18-35, 37, 38 and 40-44 were pending. The present response cancels claims 1-13, 18-35, 37, 38 and 41-44. Upon entry of the amendments, claims 14 and 40 will be pending. Applicants reserve the right to re-present the cancelled subject matter in the present application or in a continuing application.

II. Response to the Office Action.

A. Allowable Subject Matter.

Applicants note with appreciation that the Examiner has indicated that claim 14 is allowable.

B. Objection to the Abstract of the Disclosure.

The Abstract of the Disclosure was objected to as being allegedly not meeting the requirements for an abstract and for being allegedly "excessively brief". Applicants have revised the Abstract. Applicants respectfully submit that the Abstract as amended fully meets the requirements of 37 C.F.R. § 1.72. Applicants respectfully point out that the regulations require that the Abstract be a "*brief* abstract of the technical disclosure in the specification." 37 C.F.R. § 1.72 (emphasis added).

C. Objection to Claims 1, 20, 27 and 29.

The objection to claims 1, 20, 27 and 29 for containing a typographical error is moot in view of the fact that the claims in question have been cancelled.

D. Rejections of Claims 1-14, 18-35, 37, 38 and 41-42 under 35 U.S.C. § 112, first paragraph, written description requirement.

The rejection of claims 1-14, 18-35, 37, 38 and 41-42 under the written description requirement of 35 U.S.C. § 112, first paragraph is moot in view of the fact that these claims have been cancelled.

E. Rejection of Claims 1, 3, 5, 6, 8, 10-12, 19, 20, 22, 25-30, 32-34, 41 and 43-44 under 35 U.S.C. § 112, second paragraph.

The rejection of claims 1, 3, 5, 6, 8, 10-12, 19, 20, 22, 25-30, 32-34, 41 and 43-44 under 35 U.S.C. § 112, second paragraph is moot in view of the fact that these claims have also been cancelled.

F. Rejection of Claims 20-35, 37, 38 and 40-44 under 35 U.S.C. § 102(b) over Wanner.

Claims 20-35, 37, 38 and 40-44 under 35 U.S.C. § 102(b) were rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Wanner *et al.*, *Bioorg. Med. Chem. Lett.*, **2000**, *10*, 2141-2144 ("Wanner"). The rejection is moot as to claims 20-35, 37, 38 and 41-44, which have been cancelled, and is respectfully traversed as to claim 40.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). In order to establish anticipation based on inherency, however, evidence is required. "Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991). "Inherency, however, *may not be established by probabilities or possibilities*. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Id.* at 1269 (citing *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981) (quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 214 (C.C.P.A. 1939)) (emphasis added).

Wanner discusses 2-methoxyadenosine as one of the products formed in a first attempt to a synthetic route for 2-nitroadenosine. However, Wanner does not disclose that the 2-methoxyadenosine prepared therein had greater than 96% purity and the Office has cited no evidence proving that the 2-methoxyadenosine would inherently be produced in greater than 96% purity by the method of Wanner. In fact, Wanner states that the 2-methoxyadenosine prepared therein was prepared as the main product, thereby indicating that the 2-methoxyadenosine was prepared along with other products and was not pure. Wanner does not provide any indication that the 2-methoxyadenosine prepared therein was more than 96% pure.

The specification of the present application explains (on page 3, first paragraph) that 2-methoxyadenosine (also known as spongosine) is not produced in high yield or purity using the method of Wanner. At pages 3-4 of the specification the Applicants explain that the yield and purity of spongosine is limited by a number of factors:

> i) The 2-nitroadenosine pentaacetate is contaminated with TBAN. This interferes with the subsequent methoxylation and deprotection of the 2-nitroadenosine pentaacetate (this is also the case if tetramethylammonium nitrate (TMAN) is used instead of TBAN), and adversely affects the purity and yield of the spongosine product. This is particularly problematic because TBAN is amphiphilic, and so could not be removed by aqueous work-up. In addition, because of the partial solubility of 2-nitroadenosine pentaacetate in the aqueous layer, some of this may have been lost by aqueous work-up.
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> ii) The adenosine pentaacetate intermediate is produced only in low yield and purity. We found that the tetra-acetylated precursor is present as a major by-product.
>
> iii) The fifth acetate group of the penta-acetyl compounds is labile, and this results in decomposition of these compounds to tetra-acetyl compounds. For example, we purified adenosine pentaacetate by column chromatography, but there was evidence to suggest that the compound decomposed during this process. Attempts to recrystallise this compound were not successful and it was amorphous rather than crystalline in nature."

The Applicants in fact attempted to prepare spongosine on nine occasions using a procedure corresponding to that described in Wanner et al (but using sodium methoxide instead of the toxic reagent potassium cyanide for the removal of acetate groups in the final step). The procedure was very variable and not appropriate for reliable preparation of high purity spongosine. On two occasions the reaction failed and spongosine could not be detected. On three occasions the spongosine prepared was contaminated with TBAN, and on three other occasions, the spongosine was contaminated with other impurities (over 40% contamination, for example with 8-hydroxyspongosine). The Applicants were unable to obtain pure 2-methoxyadenosine using this method.

Based on the foregoing, Applicants respectfully submit that the Office has not shown that Wanner describes 2-methoxyadenosine having a purity of greater than 96%, and the rejection should therefore be withdrawn.

G. Rejections of Claim 40 under 35 U.S.C. § 102(b) over Ueeda.

Claim 40 was rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Ueeda *et al.*, *J. Med. Chem.*, **1991**, *34*, 1334-1339 ("Ueeda"). Applicants respectfully traverse the rejection.

Ueeda describes a bioassay of the A1 and A2 adenosine receptor agonist potencies of a series of 2-alkoxyadenosines, including 2-methoxyadenosine. However, Ueeda does not disclose that the 2-methoxyadenosine prepared therein had greater than 96% purity and the Office has cited no evidence proving that the 2-methoxyadenosine produced by Ueeda would inherently have been produced in greater than 96% purity.

Synthesis of the 2-alkoxyadenosines tested is described starting at page 1335, right column. The authors refer to a method of Marumoto which the chloro group of 2',3'-O-(ethoxymethylidene)-2-chloroadenosine was displaced with an alkoxide. Ueeda generated the alkoxides by adding n-butyllithium to a solution of a 5% molar excess of an alcohol in dry 1,2-diethoxyethane. The authors state that adding thoroughly dried 2',3'-O-(ethoxymethylidine)-2-chloroadenosine and heating at reflux for 5-7 days usually generated the blocked 2-alkoxyadenosine in satisfactory yield. Tritylation of the 5'-OH group was required for satisfactory yield from displacement of the chloro group by the lithium sec-alkoxides. It is stated that blocking the 2'- and 3'-OH groups was essential to prevent a major side reaction. It appears that the ethoxymethylidine nucleosides were de-blocked by refluxing in 50% acetic acid and then in ammonia.

The only specific information provided in the reference regarding the preparation of 2-methoxyadenosine appears to be in Table I. The table of Ueeda describes the UV absorption data and a melting point for the 2-methoxyadenosine, but there appears to be no disclosure in this document of the purity of 2-methoxyadenosine that was obtained >96% pure.

In addition, the Office has provided no evidence to meet its burden of showing that Ueeda's 2-methoxyadenosine would *necessarily* have been obtained >96% pure. A showing of inherent anticipation requires "extrinsic evidence [that] 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of

circumstances is not sufficient.' " MPEP 2112 (citing *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)).

Based on the foregoing, Applicants respectfully submit that the Office has not shown that Ueeda describes 2-methoxyadenosine having a purity of greater than 96%, and the rejection should therefore be withdrawn.

H. Rejection of Claims 20-35, 37, 38 and 40-44 under 35 U.S.C. § 103(a) over Wanner.

Claims 20-35, 37, 38 and 40-44 were rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Wanner. The rejection is moot as to claims 20-35, 37, 38 and 41-44, which have been cancelled, and is respectfully traversed as to claim 40.

The Office alleges that it would have been obvious to a person of ordinary skill in the art to attempt the optimization of the process described in Wanner by routine experimentation, and that this would have been expected to include improve the yields by improving the purity of intermediate and final products. The Office suggests that this would have been achieved through applying allegedly standard organic chemical methodologies including washing and/or recrystallization to improve the purity of process intermediates, or other routine experimentation to the variation of other operating variables in the process steps disclosed by Wanner.

Applicants respectfully disagree that it would have been obvious for the person skilled in the person skilled in the art to attempt to "optimize" the process of Wanner so as to result in the formation of 2-methoxyadenosine with greater than 96% purity. Not the least reason is that in the Wanner publication, 2-methoxyadenosine is only formed as an unintended and undesired product, namely the result of a side reaction in which the nitro group of the desired product (a 2-nitroadenosine) was inadvertently removed as a result of nucleophilic substitution of the nitro group under the conditions which were employed to deprotect the acetoxy groups of the penta-acetate derivative of 2-nitroadenosine. Thus, the person skilled in the art seeking to "optimize" the process disclosed by Wanner would not have had any reason even to try to prepare 2-methoxyadenosine with high purity. Instead, he would have wished to avoid its formation altogether.

In addition, the Office does not explain, except in generalities, in what way it would have been obvious for the person skilled in the art to modify the process described by Wanner to

produce 2-methyoxyadenosine with >96% purity had he wished to do so. The specification of the present application describes problems that were found by the inventors in attempting to adapt the process of Wanner to prepare pure 2-methoxyadenosine (which the reference itself does not suggest). In particular, the specification at page 11 explains that the fifth acetate group of the penta-acetyl compounds was found to be labile, and attempts to purify adenosine pentaacetate by column chromatography and recrystallization were not successful. At page 3, the specification discusses that 2-nitroadenosine pentaacetate prepared by the method of Wanner is contaminated with tetrabutylammonium nitrate (TBAN), which is amphiphilic, and so could not be removed by aqueous work-up. Futhermore, because of the partial solubility of 2-nitroadenosine pentaacetate in the aqueous layer, some of it may be lost by aqueous work-up. Thus, the Applicants explain in the specification that attempts to use Wanner's process did not sufficiently improve the yield of the 2-methoxyadenosine obtained.

Applicants surprisingly found by using benzoyl protecting groups, the purity and yield of spongosine could be greatly improved. In particular, 2-nitro-pentabenzoyl adenosine was found to have increased organic solubility, stability and crystallinity compared to 2-nitroadenosine pentaacetate (page 4, last paragraph). A particular advantage of these properties was that, in contrast to 2-nitroadenosine pentaacetate, much or all of the TBAN could be removed from 2-nitro-pentabenzoyl adenosine by aqueous work-up to obtain pure spongosine lacking the TBAN impurity. However, such a process is not remotely suggested by Wanner.

Based on the foregoing, Applicants respectfully submit that 2-methoxyadenosine with >96% purity would not have been obvious based on Wanner and Applicants therefore ask that the rejection made under 35 U.S.C. § 103(a) be withdrawn.

III. Conclusion.

Based on the foregoing, the Applicants believe that the rejections have been overcome. It is respectfully submitted that the application should be found in condition for allowance, and an early notice toward that end is earnestly solicited.

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Respectfully submitted,

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